REMARKS

Claims 1-23 are pending in the instant application. Claims 1-23 have been rejected. Claims 2-6 and 21-23 have been canceled. Claims 1, 11, 13 and 14 have been amended. No new matter has been added by these amendments to the claims. Reconsideration is respectfully requested in light of these amendments and the following remarks.

I. Double Patenting Rejection

Claim 6 has been rejected under 35 U.S.C. 101 as claiming the same invention as that of claim 1 of U.S. Patent 5,872,242. The issued claims in this patent claim compositions and methods of antisense oligonucleotides targeted to human N-ras and comprising specific SEQ ID NO's. The claimed sequences, 44, 45, 46, 47, 49 and 52, are identical to sequences disclosed in the instant specification and also referred to as SEQ ID NOs: 44, 45, 46, 47, 49 and 52. The 5,872,242 patent, however, does not claim antisense oligonucleotides to human Ki-ras. Applicants have amended or canceled all claims of the instant application that refer to antisense oligonucleotides targeted to ras forms other than Ki-ras.

Accordingly, withdrawal of this rejection is respectfully requested.

II. Obviousness-Type Double Patenting

Claims 1, 4, 5 and 7-22 have been rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-8 of U.S. Patent 5,872,242. The Examiner suggests that although the conflicting claims are not identical, they are not patentably distinct from each other because the species claims of U.S. Patent 5,576,208 anticipate the larger genus claims 1, 4, 5 and 7-22 of the current application. Additionally, claims 1, 2, 5 and 7-23 have been rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-4 of U.S. Patent 5,576,208. Again, the Examiner suggests that although the conflicting claims are not identical, they are not patentably distinct from each other because the species claims of U.S. Patent 5,576,208 anticipate the larger genus claims 1, 2, 5 and 7-23 of the current application. Since the instant invention and the patents cited are commonly owned, a terminal disclaimer in compliance with 37 CFR 1.321 has been filed herewith. Withdrawal of this rejection to the claims is respectfully requested.

III. Rejection of Claims Under 35 U.S.C. 112, First Paragraph

Claims 1-5 and 7-23 have been rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors had possession of the claimed invention at the time of filing. Specifically, the Examiner suggests that the specification teaches antisense oligonucleotides which function to inhibit ras where the claims are drawn to an oligonucleotide "which is capable of inhibiting ras expression" while the specification teaches the functional characteristic of hybridizing to a transcript and preventing translation of the transcript. The Examiner goes on to suggest that it is well known in the art that only a portion of complementary nucleic acid sequences are effective at inhibiting expression of a gene and effective sequences cannot be predicted and must be identified experimentally. The Examiner cites several references to support this position. Applicants respectfully traverse this rejection of the claims.

Applicants have amended the claims to recite specific antisense oligonucleotides targeted to human Ki-ras. The sequences now claimed have been shown to have specific activity to inhibit expression of Ki-ras. As acknowledged by the Examiner, showing of

activity is evidence of possession of the instant invention. As the claims are now drawn to sequences that affect human Ki-ras that are taught at pages 35-38 and Figure 6 of the instant specification as filed, withdrawal of this rejection is respectfully requested.

IV. Rejection of Claims Under 35 U.S.C. 103(a)

Claims 1, 3 and 5-22 have been rejected under 35 U.S.C. 103(a) as being unpatentable over Bos, Daaka et al., Hall et al., and Saison-Behmoaras et al., each in view of Uhlmann et al, Agrawal et al., and Inoue et al., and further in view of Smith. The Examiner suggests that the invention as a whole was *prima facie* obvious because Bos discloses antisense oligonucleotides to human H-ras and Ki-ras and to specific regions of ras genes that are mutated in the activated forms, because Hall et al. teach the sequence of N-ras from which specific antisense molecules are derived, because Daaka et al. teach antisense molecules to the translation initiation site of H-ras gene and their use to inhibit expression of H-ras, and because Saison-Behmoaras et al. teach oligonucleotide that specifically hybridize to the codon 12 region of H-ras and methods to inhibit gene expression. The teaching of these primary references is suggested by the Examiner to be supplemented by the teaching of modification to antisense oligonucleotides by Uhlmann

et al., Agrawal et al., and Inoue et al., while Smith et al. teach use of antisense compounds against oncogenes or genes that are differentially expressed in tumor cells as treatment for cancer. The Examiner goes on to suggest that motivation is provided by Saison-Behmoaras et al., Daaka et al., and Bos et al. Applicants respectfully traverse this rejection.

At the outset, the claims have been amended to recite specific sequences taught in the specification to have activity to modulate expression of human Ki-ras. None of these specific antisense oligonucleotide sequences is taught or suggested by any of the prior art references.

Bos et al. (U.S. Patent 4,871,838) disclose antisense oligonucleotides to human H-ras and Ki-ras that have from 12 to 43 nucleotides. However, the claimed sequences are not taught or suggested. Hall and Brown (1985) teach the sequence of human N-ras and mutations to codons 12 and 61. Nowhere does this paper teach or suggest antisense to Ki-ras, or any of the antisense oligonucleotide sequences of the instant invention. Daaka et al. teach antisense oligonucleotides to the translation initiation codon of H-ras. However, nowhere does this reference teach or suggest antisense compounds to Ki-ras, or any of the antisense oligonucleotide sequences of the instant invention.

Saison-Behmoaras et al. (1991) teach short modified antisense oligonucleotides targeted to H-ras and the 12th codon region as a target within the H-ras gene. Again, however, nowhere does this paper teach or suggest antisense compounds to Ki-ras, or any of the antisense oligonucleotide sequences of the instant invention.

Therefore, these primary references fail to teach or suggest the claims as amended. The secondary references cited by the Examiner fail to overcome the deficiencies of the primary prior art references.

Uhlmann et al. discloses modifications to antisense oligonucleotides such as are taught in the instant invention. However, nowhere does this paper teach or suggest antisense oligonucleotides to human ras genes, nor any sequences taught by the instant invention.

Inoue et al. and Agrawal et al. teach ways to confer sensitivity and resistance to RNase H in cells. Nowhere do these papers teach or suggest antisense oligonucleotides to human ras genes, nor any sequences taught by the instant invention.

Finally, Smith et al. disclose antisense oligonucleotides as a tool for treatment of cancer. However, nowhere does this paper teach or suggest antisense oligonucleotides to human ras genes, nor any sequences taught by the instant invention.

To establish a *prima facie* case of obviousness, three basic criteria must be met. MPEP 2143. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art must teach or suggest all claim limitations. Clearly, the combination of prior art cited fails to teach or suggest the limitations of the claims as amended, which claim specific antisense oligonucleotide sequences targeted to human Ki-ras, and thus cannot render the instant claimed invention obvious. Withdrawal of this rejection is therefore respectfully requested.

V. Conclusion

Applicants believe that the foregoing comprises a full and complete response to the Office Action of record. Accordingly, favorable reconsideration and subsequent allowance of the pending claims is earnestly solicited.

Attached hereto is a marked-up version of the changes made to the specification and claims by the current amendment. The

attached page is captioned "Version with Markings to Show Changes Made."

Respectfully submitted,

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the claims:

Claims 2-6 and 21-23 have been canceled.

The claims have been amended as follows:

1. (amended) An oligonucleotide 8 to 30 nucleotides in length which is targeted to a nucleic acid encoding human Ki-ras ~~and which~~, wherein said oligonucleotide is capable of inhibiting Ki-ras expression, and wherein said oligonucleotide comprises at least an 8-nucleobase portion of SEQ ID NO: 20, 21, 22, 26, 28, 31, 32 or 33.

11. (amended) A method of modulating the expression of human Ki-ras comprising contacting tissues or cells containing a human Ki-ras gene with an effective amount of an oligonucleotide of claim 1 whereby expression of Ki-ras is modulated.

13. (amended) A method of preventing or treating a condition arising from the activation of a Ki-ras oncogene comprising contacting an animal suspected of having a condition arising from the activation of a Ki-ras oncogene with an effective amount of an

oligonucleotide of claim 1, whereby said condition is prevented or treated.

14. (amended) The method of claim 13 wherein said activation of a Ki-ras oncogene is abnormal expression of a Ki-ras oncogene.